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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
2421 N.W. 41ST STREET
SUITE A-1
GAINESVILLE, FL 326066669

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| EXAMINER |
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HARRIS, ALANA M

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| ART UNIT | PAPER NUMBER |
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1642

DATE MAILED: 07/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/070,569

Applicant(s)

MURAMATSU ET AL.

Examiner

Alana M. Harris, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 May 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) 10-12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 13 and 14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☒ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9112
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I (claims 1-9, 13 and 14) in Paper No. 10, received May 12, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-14 are pending.

Claims 10-12, drawn to non-elected inventions are withdrawn from examination.

Claims 1-9, 13 and 14 are examined on the merits.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention, a method to which the claims are directed.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-9, 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

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convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants broadly claim a method for detecting early cancer comprising measuring the level of midkine (MK) or a fragment thereof. The written description in this instant case has not been sufficiently set forth. Applicants' specification has not defined a sequence or structurally characterized the MK provided in the claimed invention. Therefore the written description is not commensurate in scope with the claims broadly drawn to a method for detecting early cancer comprising measuring the level of MK. Applicants are not in possession of any and all MK molecules which encompass molecules from any species of animal, as well as mutant MK, see page 5, lines 2 and 3. Although Applicants establish that the MK encompassed by the broad claims is a full-length MK and a fragment comprising an amino acid sequence, there is no clear description (i.e. SEQ ID identifier, number of amino acid residues, etc). Applicants also set forth that the sequence can comprise an amino acid sequence of an arbitrary length having biological activity of MK, this disclosure is nebulous in characterization of MK, see bridging paragraph of pages 4 and 5.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Applicant is

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reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Applicants are not required to disclose every species encompassed by a genus. For example as indicated in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Applicants seem to only be in possession of one species, human midkine polypeptide, which has not been defined by a SEQ ID number or structure. Applicants are not permitted to claim all proteins that are encompassed by the claims, hence not entitled to the wide breadth of the claims at issue. As Applicants' claims are written they encompass variants, as well as sequences yet to be discovered. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. One skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

There is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at

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Volume 63, Number 114, pages 32639-32645. Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph.

6. Claims 1-9, 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting cancer and assessing cancer prognosis comprising the steps of measuring the level of human midkine protein in a biological sample, does not reasonably provide enablement for a method for detecting cancer and assessing cancer prognosis comprising the measuring the level of a midkine mutant or a midkine fragment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification evidences a method of measuring the serum MK level in hepatocellular carcinoma and gastric cancer patients at stages I to IV in Figures 1-8. Figures 9 and 10 exemplify a method of measuring the urine MK level from colon, hepatocellular and gastric cancer patients and correlations were made between urine MK values in cancer patients and cancer stages, see corresponding captions on page 13, lines 9-20. These examples seem to exemplify Applicants use of an antibody that recognized human full-length MK and not mutants and arbitrary fragments of MK. The specification does not provide enabling disclosure that evidences a method for detecting cancer comprising measuring a fragment of MK, implementing the said method with an antibody that recognizes a fragment or mutant of MK or a method of assessing cancer

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prognosis using the said fragments and undefined mutant and variant MK molecules. For the discriminate diagnosis of a cancer it would seem that standards, such as the probing tools would need clear characterization, structurally and functionally to be useful. The specification does not provide sufficient guidance as to which of the amino acids may be changed in mutant MK of arbitrary amino acid length while MK structural or functional activity and specificity is retained.

For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). For example, Li et al. (PNAS 77: 3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). Because of this lack of guidance, the extended experimentation that would be required to determine which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo et al.; in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.). It would require an undue amount of experimentation for one of skill in the art to facilitate the claimed invention for the crucial analysis of prognostication and detection.

The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes, which can be made in the MK amino acids, still maintain biological activity

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or structural specificity of MK molecules by MK antibodies is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-9, 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1, 9 and 13 are vague and indefinite in the recitation "the level of midkine". It is not clear what form of midkine is to be detected in the method. It is not clear if one should detect the level of gene expression, mRNA, DNA or protein.

Accordingly, the metes and bounds cannot be determined.

b. Claims 1, 2, 4, 6 and 9 are vague and indefinite in the recitation "early cancer". Applicants set forth in the background art of the specification that "[e]arly cancer is basically symptomless.", see page 1, line 16. Given this admission it not clear how one of ordinary skill in the art would be able to differentiate between a "normal" person without cancer, who is also symptomless and a person who is deemed as having early cancer. The term "early" does not aid in classifying or staging the cancer.

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c. Claim 13 is vague and indefinite in the method steps. There is no correlation step stating what the measured level of midkine, a fragment or both in a biological sample is compared to in order to assess a cancer prognosis. Furthermore, the phrase "correlating the measured level obtained from step a) to cancer prognosis, to thereby assess prognosis" is not further clarifying step b.

And while all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is practiced. The method steps should at least include reagents necessary for the assay, a detection step in which the reaction products are quantitated or visualized and a correlation step describing how the results of the assay allows the determination of for example, the prognosis of a disease.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 9 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Ye et al. (British Journal of Cancer 79(1): 179-184, January 1999/ Reference R2 from IDS Paper number 9). Ye discloses a method for examining the status of MK mRNA in adenomas with moderate- and severe-grade dysplasia, carcinomas and corresponding

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normal tissue, by means of Northern blotting. The MK expression level was significantly more elevated in adenomas than in normal tissues. The authors concluded that there is "...the association of elevated MK expression with early stage of carcinogenesis in humans", see Abstract. "[T]he level of MK mRNA was elevated from the adenoma with dysplasia stage to the advanced carcinoma stage", see page 181, column 1, first full paragraph.

"MK [protein] staining was observed in adenomas with moderate- and severe-grade dysplasia and in carcinomas, but not in the normal colorectal mucosa or adenomas with mild-grade dysplasia (Figure 3 and Table 1)", see page 181, bridging paragraph of columns 1 and 2. Ye surmised that MK RNA expression was elevated from the adenoma stage to the carcinoma stage, and MK protein expression revealed by immunohistochemistry exhibited a similar profile (Table 2), see page 181, column 2, last paragraph before Discussion section.

11. Claims 1-5, 9, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Aridome et al. (Jpn. J. Cancer Res. 86: 655-661, 1995/ Reference R1 from IDS, Paper number 12). Aridome discloses a method of examining the expression of the MK gene in specimens of human carcinomas from gastrointestinal organs, namely gastric and hepatocellular. The MK mRNA level was higher in cancer specimens than in the corresponding non-cancerous tissues. The increased expression of the MK gene in gastric carcinoma was significantly more prominent in well and

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moderately differentiated adenocarcinomas than in poorly differentiated adenocarcinomas, see Abstract.

The findings presented in the anticipatory studies clearly indicate that the MK gene expression is increased in a variety of human gastrointestinal carcinomas. The liver did not express MK, however cancer of the liver newly expressed MK, see page 659, first sentence of Discussion section; page 660, column 2, paragraph 2.

Immunohistochemical staining of human rectal carcinoma and a negative control was conducted utilizing anti-MK antibodies, see page 659, Figure 2.

12. Claims 1-7, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsutsui et al (Cancer Research 53:1281-1285, March 15, 1993/ Reference R7 from IDS, Paper number 12). Tsutsui discloses a method of analyzing MK mRNA levels in stomach, colon, lung and esophageal carcinomas, see Abstract. MK mRNA expression was assessed in surgically removed specimens from hepatocellular carcinomas, see Figure 4C, lanes 3-6. High levels of MK gene were expressed in hepatocellular, stomach, lung, colon and esophageal carcinomas. MK gene expression level was much lower in normal tissues, see page 1283, column 2, first full paragraph.

13. Claims 1, 4, 5, 8, 9, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Muramatsu et al. (J. Biochem. 119: 1171-1175, 1996/ Reference R6 from IDS, Paper number 12). Muramatsu discloses a method of detecting early cancer and assessing MK expression. MK protein was evaluated in sera from patients with

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hepatocellular carcinomas. The method involved an enzyme-linked immunoassay and using an affinity-purified anti-MK antibody, see Abstract. The MK levels in sera of normal human subjects were either undetectable or less than 0.6ng/ml, whereas in more than half the hepatocellular carcinoma patients MK was detectable in sera in the range of 0.6-8ng/ml, see bridging paragraph of pages 1173 and 1174; page 1174, Figure 5.

14. Claims 1 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakagawara et al. (Cancer Research 55(8): 1792-1797, April 15, 1995/ Reference R1 from IDS, Paper number 9). Nakagawara discloses a method of detecting MK mRNA in primary neuroblastomas independent of disease stage, see page 1792, column 2, paragraph before Materials...section. MK was expressed differentially in advanced tumors, see Figure 1 from page 1793. MK expression was associated with a difference in survival rate and "patients with favorable stages (I, II, and IV-S) had a better prognosis than those with advanced stages", see bridging paragraph of pages 1794 and 1795.

15. Claims 1-9, 13 and 14 rejected under 35 U.S.C. 102(a) as being anticipated by Ikematsu et al. (British Journal of Cancer 83(6): 701-706, September 2000/ Reference R3 from IDS, Paper number 12). Ikematsu discloses a method yielding the result that serum MK levels are increased in patients with stage I gastric, hepatocellular and lung carcinomas, see Table 1 on page 702. Specifically, "in the case of gastric carcinoma

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and lung carcinoma, patients with stage I carcinoma...showed elevated serum MK levels", see summary. An enzyme-linked immunoassay utilizing a combination of rabbit and chicken antibodies revealed that serum MK level in the controls was lower than the serum MK levels in the cancer patients, see summary. The finding implied that MK may be useful in detecting certain carcinomas at early stages, see page 706, last paragraph.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. Claims 1-5, 8, 9, 13 and 14 rejected under 35 U.S.C. 103(a) as being unpatentable over Aridome et al. (Jpn. J. Cancer Res. 86: 655-661, 1995/ Reference R1 from IDS, Paper number 12), in view of Muramatsu et al. (J. Biochem. 119: 1171-1175, 1996/ Reference R6 from IDS, Paper number 12). The teachings of Aridome have been presented in the 102(b) rejection above. Aridome does not teach the biological sample is serum or urine.

However, Muramatsu teaches a method of measuring MK levels in sera from normal human subjects and patients with hepatocellular carcinomas, see Muramatsu, page 1173, column 2, Determination...section. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to evaluate sera

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from patients with gastric cancer using an enzyme-linked immunoassay an affinity-purified anti-MK antibody to effectively diagnose and predict cancer. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the listed teachings because Muramatsu assessed that "strong expression of MK mRNA was correlated with a worse prognosis in patients with neuroblastomas", which provided the impetus to conduct their study and would lead one to assess MK levels in sera from patients with other cancers, see page 1171 bringing sentence of columns 1 and 2.

18. Claims 1-9, 13 and 14 rejected under 35 U.S.C. 103(a) as being unpatentable over Tsutsui et al (Cancer Research 53:1281-1285, March 15, 1993/ Reference R7 from IDS, Paper number 12), in view of Muramatsu et al. (J. Biochem. 119: 1171-1175, 1996/ Reference R6 from IDS, Paper number 12). The teachings of Tsutsui have been presented in the 102(b) rejection above. Tsutsui does not teach the biological sample is serum or urine and the implementation of an enzyme-linked immunoassay with an affinity-purified anti-MK antibody.

However, Muramatsu teaches a method of measuring MK levels in sera from normal human subjects and patients with hepatocellular carcinomas, see Muramatsu, page 1173, column 2, Determination...section. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to evaluate sera from patients with stomach, colon, lung and esophageal carcinomas using an enzyme-linked immunoassay an affinity-purified anti-MK antibody to effectively diagnose and

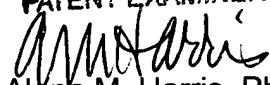
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predict cancer. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the listed teachings because Muramatsu assessed that "strong expression of MK mRNA was correlated with a worse prognosis in patients with neuroblastomas", which provided the impetus to conduct their study and would lead one to assess MK levels in sera from patients with other cancers, see page 1171 bringing sentence of columns 1 and 2.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

ALANA HARRIS
PATENT EXAMINER

Alana M. Harris, Ph.D.
July 26, 2003